Remarks

Applicants have canceled claims 11, 13, 17-18, 20, 22-23, 25-33, 47-50, and 52-54 without prejudice or disclaimer. Applicants have also amended claims 24 and 46 without prejudice or disclaimer to cancel sub-parts 24(b)-(k) and 46(b)-(d); Applicants have added new claims 106-148 to correspond to the subject matter of claims 24(b)-(k) and 46(b)-(d). Further, claims 36 and 57 have been amended to insert the article "an" prior to "immunoglobulin," and claim 51 has been amended to remove the phrase "further comprises," both without prejudice or disclaimer. Attached hereto is a marked-up version of the changes made by the current amendments, captioned "Version With Markings To Show Changes Made." The amendments are fully supported by the specification and claims as originally filed, and thus no new matter has been added.

Claims 24, 34-46, 51, and 55-148 will be pending upon entry of these amendments.

I. Objection to the Title

The Examiner has objected to the title because it allegedly is not descriptive. *See* Paper No. 14, page 4, lines 20-21.

In response, Applicants have amended the title to more clearly indicate that the instant claims are directed to "Polynucleotides Encoding Connective Tissue Growth Factor 4." Applicants submit that this amendment addresses the Examiner's objection, and that the title as amended fully complies with 37 C.F.R. § 1.72(a). Accordingly, it is respectfully requested that the Examiner's objection to the title be reconsidered and withdrawn.

II. Objection to the Claims

The Examiner has objected to the claims as allegedly encompassing multiple patentably distinct inventions, and has required amendment of the claims to include only the elected invention. *See* Paper No. 14, page 4, lines 23-25.

Applicants preliminarily note that the restriction requirements in Paper Nos. 6 and 10 have been traversed in Applicants' responses of January 25, 2001 and August 15, 2001, respectively; the Examiner acknowledged such traversals in Paper Nos. 10 and 14, respectively. Thus, Applicants retain the right to petition from the restriction requirements under 37 C.F.R. § 1.144.

However, Applicants have amended the claims that included non-elected inventions, as required by the Examiner. In particular, Applicants have amended claim 24 to include only former sub-part (a); new claims 106-129, directed to former sub-parts (b)-(k), have been added to retain the non-elected subject matter removed from claim 24. Likewise, Applicants have amended claim 46 to include only former sub-part (a); new claims 130-148, directed to former sub-parts (b)-(d), have been added to retain the non-elected subject matter removed from claim 46.

Applicants submit that these amendments fully address the Examiner's objection to the claims. Accordingly, it is respectfully requested that the Examiner's objection to the claims be reconsidered and withdrawn.

III. Non-Consideration of References AE-AI

The Examiner has indicated that References AE-AI, submitted with the Information Disclosure Statement filed January 25, 2001, have not been considered, as

they are allegedly "merely sequences with no explanation of relevance or alignment with the disclosed sequences, such that relevancy to the claimed invention cannot be assessed." Paper No. 14, page 5, lines 1-3.

In response, Applicants respectfully note that neither 37 C.F.R. § 1.97 or § 1.98 provide that failure to provide an explanation of relevance or an alignment for sequence information cited in an Information Disclosure Statement is a proper basis for failing to consider such information. *See also* M.P.E.P. § 609(III). Accordingly, Applicants respectfully submit that References AE-AI were properly submitted and should have been considered by the Examiner.

However, as an explanation of the relevancy of References AE-AI, Applicants point out that the references were cited as category X/Y documents by Examiner Spector in the International Search Report (Reference AS submitted herewith) for International Application PCT/US99/12150, which is a counterpart international application of the instant U.S. application. *See* 37 C.F.R. § 1.56(a)(2). As a courtesy to the Examiner, References AE-AI have again been cited on the Information Disclosure Statement enclosed herewith; a copy of each reference is also enclosed.

Accordingly, Applicants respectfully ask that the Examiner consider References AE-AI, and return an initialed copy of Form PTO/SB/08 with the next Office Action.

IV. Rejections Under 35 U.S.C. §§ 101 and 112, First Paragraph

The Examiner has rejected claims 24, 25, 34-47, 51, and 55-66 under 35 U.S.C. § 101 because the invention is allegedly not supported by either a credible, specific,

substantial asserted utility or a well established utility. *See* Paper No. 14, pages 5-8. In particular, the Examiner contends that:

> The assertion that the disclosed CTGF-4 would have biological activities similar to known HBGF cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities.

The Examiner has further rejected claims 24, 25, 34-47, 51, and 55-66 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention, based on the supposed lack of either a credible, specific, substantial asserted utility or a well established utility. *See id.*, page 8.

Applicants respectfully disagree and traverse these rejections.

Preliminarily, Applicants note that the Examiner has acknowledged that the specification asserts utilities for CTGF-4 (Paper No. 14, page 5, lines 20-23, page 6, lines 7-8, and page 7, lines 5-6). In particular, the specification teaches the use of the claimed invention in diagnostic methods for detecting disorders related to connective tissue, such as cancer, as well as the use of the claimed invention in the treatment of cancer. *See, e.g.,* Specification at pages 1, 73-75, and 125-126.

It is well established that "[a]n applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. 101." M.P.E.P. § 2107.02(III)(A) at 2100-39; *see also In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). Thus, the burden is on the Examiner to establish that it is more likely than not that a person of ordinary skill in the art would not consider the utility asserted by Applicants to be specific, substantial, and credible. *See* M.P.E.P. § 2107 at 2100-30. Such a *prima facie* showing must contain (1) an explanation that clearly sets

forth the reasoning used in concluding that the asserted utility for the claimed invention is not specific, substantial, and credible; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. *See id.* Moreover, the Examiner must establish why it is more likely than not that one of ordinary skill in the art would doubt *(i.e.,* "question") the truth of the statement of utility. *See id.*; *see also In re Cortright,* 49 U.S.P.Q.2d 1464, 1466 (Fed. Cir. 1999); *In re Brana,* 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Indeed, the Utility Guidelines note that:

> Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong," even when there may be reason to believe that the assertion is not entirely accurate. Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.
>
> M.P.E.P. § 2107.02 at 2100-40.

For the reasons set forth below, the Examiner has not met this burden, and thus the rejection of the claims for lack of utility under 35 U.S.C. § 101 must be withdrawn.

In particular, the Examiner bases the allegation that the asserted utility is not credible, substantial, and specific on references discussing different proteins that allegedly support the assertion that "[o]ne cannot rely upon structural similarity alone to determine functionality." Applicants respectfully disagree with the Examiner's conclusion, and note that those of skill in the art routinely rely on homology as predictive of protein function. Further, evidence directed to the predictability of function based on proteins distinct from the instant protein, rather than close family members such as CTGF or HBGF, cannot

But then they test!

support the instant rejection. Indeed, M.P.E.P. § 2107 notes that the Examiner should consider "the closest prior art," yet the Examiner has presented no evidence directed to CTGF or HBGF. The Examiner has made no showing, for example, that the asserted utility is inconsistent with the function of other CCN family members, such as connective tissue growth factor [CTGF], Cyr61/Cef10, and neuroblastoma overexpressed gene product [Nov]. Nor has the Examiner identified a reference suggesting that CTGF-4 has activities that do not correlate with the asserted utilities. Thus, the Examiner has not met the required burden to show that Applicants' asserted utility is not credible.

Additionally, Applicants respectfully direct the attention of the Examiner to the post-filing date references Xu et al., Genes & Development, 14: 585-595 (2000), Xie et al., Cancer Research, 61: 8917-8923 (December 2001), Desnoyers et al., The Journal of Biological Chemistry, 276(50): 47599-47607 (December 2001), Su et al., Genes & Development, 16: 46-57 (2002), and Tanaka et al., Oncogene, 20(39): 5525-32 (September 2001) (submitted herewith as references AK-AW with the enclosed Information Disclosure Statement). Xu et al. disclose that WISP-1 (which is identical to CTGF-4) overexpression in rat kidney fibroblast cells (NRK-49F) induced morphological transformation, accelerated cell growth, enhanced saturation density. Moreover, Xu et al. also disclose that subcutaneous injection of WISP-1 into nude mice induced tumor formation. Xie et al. disclose that elevated levels of WISP-1 are found in primary breast cancers. Desnoyers et al. disclose that WISP-1 binding to the stroma of colon tumors and to fibroblast-like cells was modulated by decorin and biglycan. Su et al. disclose that WISP-1 activates the Akt/PKB anti-apoptotic signaling pathway. Tanaka et al. disclose that a variant of WISP-1 was found to be overexpressed in scirrhous gastric carcinoma.

Not asserted util ?

Thus, all the above references suggest that CTGF-4 acts to promote and contribute to tumorigenesis upon binding to cancerous cells or cells with fibroblast phenotype. Because the polynucleotide sequence of WISP-1 is identical at 1003 of 1005 nucleotides over the open reading frame encoded by nucleic acids 3 to 1007 of SEQ ID NO:1, and the polypeptide sequence is identical at 335 of 335 amino acids to the sequence of SEQ ID NO:2, the observations described above support the credibility of Applicants' asserted utility for CTGF-4.

Indeed, the Patent Office has stated that utility can exist for therapeutic inventions "despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition." M.P.E.P. § 2107.01(III). "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana,* 51 F.3d 1560, 1568 (Fed. Cir. 1995) (emphasis added). Indeed, there is no need to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. *See* M.P.E.P. §§ 2107.01(III) and 2701.03. All that is required of Applicants is that there be a reasonable correlation between the biological activity and the asserted utility, as is clearly present in this case. *See Nelson v. Bowler*, 626 F.2d 853, 857 (C.C.P.A. 1980).

Applicants point out that subsequently-generated data (*e.g.*, Xu et al., Xie et al., Desnoyers et al., Su et al., and Tanaka et al.) can be used to support the credibility of a

utility asserted in the specification. As the Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n.19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. at 224 n.4, 169 U.S.P.Q. at 370 n.4. Indeed, the Utility Examination Guidelines in the M.P.E.P. specifically contemplate the use of such additional data:

> In such a case, the examiner should challenge the use and require sufficient evidence of operativeness. The purpose of this authority is to enable an applicant to cure an otherwise defective factual basis for the operability of an invention. Because this is a curative authority (e.g., evidence is requested to enable an applicant to support an assertion that is inconsistent with the facts of record in the application), Office personnel should indicate not only why the factual record is defective in relation to the assertions of the applicant, but also, where appropriate, what type of evidentiary showing can be provided by the applicant to remedy the problem.
>
> *See* M.P.E.P. § 2107.02(V) at 2100-41 to 42.

Thus, Applicants have shown that CTGF-4 has biological activities that are reasonably correlated with the asserted utilities, as discussed above. Thus, the only reasonable conclusion that can be reached based on the data and assertions of utility in the specification, supported by Xu et al., Xie et al., Desnoyers et al., Su et al., and Tanaka et al., is that the present invention is useful for the purposes asserted in the specification, namely modulating mitogenic activity of fibroblasts and tumors. Accordingly, even assuming *arguendo* that the Examiner has made a *prima facie* showing that Applicants' asserted utility is not specific, substantial, or credible, Applicants respectfully submit that the *prima facie* showing has been rebutted, and that the presently claimed invention possesses specific, substantial, and credible utilities which constitute patentable utilities

Where in spec?

under 35 U.S.C. § 101. In view of the above, Applicants respectfully request that the Examiner's prior rejection of the claims under 35 U.S.C. § 101 be reconsidered and withdrawn.

Further, the Federal Circuit and its predecessor determined that the utility requirement of 35 U.S.C. § 101 and the how to use requirement of 35 U.S.C. § 112, first paragraph, have the same basis, *i.e.*, the disclosure of a credible utility. *See In re Brana*, 51 F.3d 1560, 1564, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995); *see also* M.P.E.P. § 2107(IV). As discussed above, the specification teaches specific and well-established utilities of the claimed invention, thereby enabling the skilled artisan to use the claimed polynucleotides. Since the specification teaches how to use the claimed polynucleotides with only routine experimentation and the specification describes specific and immediate utilities for the claimed invention, Applicants submit that the full scope of the claims is enabled. Accordingly, it is respectfully requested that the Examiner's rejection of the claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

V. Rejections of the Claims Under 35 U.S.C. § 112, Second Paragraph

A. Claims 34-36 and 55-57

The Examiner has rejected claims 34-36 and 55-57 under 35 U.S.C. § 112, second paragraph as being "indefinite for failing to indicate the relationship between the recited structural elements". *See* Paper No. 14, page 8, lines 27-28. In particular, the Examiner alleges that:

> In claim 34, it is not clear whether the "heterologous sequence" is attached at an end or might be internally inserted. In claims 35 and 36, it is not clear whether applicants intend an operable attachment that would produce a

fusion protein, or merely that the two recited portions be present on the same vector. Claims 55-57 are similarly indefinite.

Paper No. 14, page 8, line 29 to page 9, line 4.

In response, Applicants respectfully disagree and traverse. While claims 34 and 55 encompass polynucleotides (of claim 24 or 46, respectively) with a heterologous polynucleotide attached at an end or internally inserted, merely because the claims encompass both relationships does not render them indefinite. Likewise, although claims 35 and 56 encompass heterologous polynucleotides that are operably attached to the instant polynucleotides to produce a fusion protein, or without such an operable attachment (*e.g.*, as a selectable marker on a vector), the claims are not indefinite. The breadth of a claim is not to be equated with indefiniteness. *See* M.P.E.P. § 2173.04; *In re Miller*, 441 F.2d 689, 169 U.S.P.Q. 597 (C.C.P.A. 1971). Applicants should not be required to present separate claims, since one of skill in the art would recognize (as the Examiner did) that claims encompass both embodiments. Thus, since claims 34-35 and 55-56 have been set forth with "a reasonable degree of particularity and distinctness," 35 U.S.C. § 112, second paragraph has been fully complied with. *See* M.P.E.P. § 2173.02. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the instant rejection.

With respect to claims 36 and 57, the Examiner contends that it is unclear as to which immunoglobulin the claims refer, and suggests the insertion of the article "an" prior to the term "immunoglobulin" to overcome the instant rejection. In response, while Applicants disagree and assert that the claims fully comply with 35 U.S.C. § 112, second paragraph, claims 36 and 57 have been amended as requested by the Examiner. Accordingly, Applicants submit that the Examiner's rejection of claims 36 and 57 under

35 U.S.C. § 112, second paragraph has been obviated, and respectfully request that the rejection be reconsidered and withdrawn.

B. The Term "Further Comprises"

The Examiner has rejected claims 47 and 51 under 35 U.S.C. § 112, second paragraph as being indefinite for reciting the term "further comprises". See Paper No. 14, page 9.

In response, while Applicants disagree with the instant rejection, Applicants note that claim 47 has been canceled, and claim 51 has been amended without prejudice or disclaimer to remove the language objected to by the Examiner. Accordingly, the instant rejection has been obviated, and Applicants respectfully request that the rejection of claims 47 and 51 under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Conclusion

Entry of the above amendment is respectfully solicited. In view of the foregoing remarks, Applicants believe that this application is now in condition for allowance, and an early notice to that effect is urged. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for in the Petition for an Extension of Time

submitted concurrently herewith, such an extension is requested and the appropriate fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: April 5, 2002

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PATENT & TRADEMARK OFFICE

VIA HAND DELIVERY APRIL 5, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Young et al. Attorney Docket No.: PF467

Application Serial No.: 09/325,019 Art Unit: 1647

Filed: June 3, 1999 Examiner: Spector, L.

Title: Polynucleotides Encoding Connective Tissue Growth Factor-4 (as amended)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 24, 36, 46, 51, and 57 have been amended as follows, without prejudice or disclaimer:

24. (Once amended) An isolated nucleic acid molecule comprising a polynucleotide ~~selected from the group consisting of:~~

~~(a) a polynucleotide~~ encoding amino acid residues 1 to 335 of SEQ ID NO:2~~,~~;

~~(b) a polynucleotide encoding amino acid residues 15 to 84 of SEQ ID NO:2;~~

~~(c) a polynucleotide encoding amino acid residues 89 to 154 of SEQ ID NO:2;~~

~~(d) a polynucleotide encoding amino acid residues 184 to 228 of SEQ ID NO:2;~~

~~(e) a polynucleotide encoding amino acid residues 241 to 316 of SEQ ID NO:2;~~

~~(f) a polynucleotide encoding amino acid residues 39 to 55 of SEQ ID NO:2;~~

~~(g) a polynucleotide encoding amino acid residues 101 to 121 of SEQ ID NO:2;~~

~~(h) a polynucleotide encoding amino acid residues 194 to 213 of SEQ ID NO:2;~~

~~(i) a polynucleotide encoding amino acid residues 264 to 280 of SEQ ID NO:2;~~

~~(j) a polynucleotide encoding amino acid residues 241 to 335 of SEQ ID NO:2; and~~

~~(k) a polynucleotide complementary to any polynucleotide (a) through (j), above.~~

36. (Once amended) The isolated nucleic acid molecule of claim 35 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.

46. (Once amended) An isolated nucleic acid molecule comprising a first polynucleotide 90% or more identical to a second polynucleotide ~~selected from the group consisting of:~~

~~(a) a polynucleotide~~ encoding amino acid residues 1 to 335 of SEQ ID NO:2~~;~~

~~(b) a polynucleotide encoding amino acid residues 15 to 84 of SEQ ID NO:2;~~

~~(c) a polynucleotide encoding amino acid residues 89 to 154 of SEQ ID NO:2; and~~

~~(d) a polynucleotide encoding amino acid residues 241 to 335 of SEQ ID NO:2~~.

51. (Once amended) The isolated nucleic acid molecule of claim 46 wherein said ~~which further comprises a~~ first polynucleotide is 95% or more identical to ~~a~~ said second polynucleotide ~~encoding amino acid residues 1 to 335 of SEQ ID NO:2~~.

57. (Once amended) The isolated nucleic acid molecule of claim 56 wherein the heterologous polypeptide is the Fc domain of an immunoglobulin.